UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/359,300	07/21/1999	MONTO H. KUMAGAI	08010137US07	2643

25871 7590 12/24/2003

SWANSON & BRATSCHUN L.L.C.
1745 SHEA CENTER DRIVE
SUITE 330
HIGHLANDS RANCH, CO 80129

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 12/24/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/359,300	KUMAGAI ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *45,60-65 and 67-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *45,60-65 and 67-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of a supplemental amendment, filed 10/1/2003, in which several claims were amended (claims 45, 64-65). Claims 45, 60-65, 67-70 are pending in the instant application.

Any rejection of record not addressed herein is withdrawn. This action is not final as there are new grounds of rejection presented herein that were not necessitated by applicants' amendment of the claims in the response filed 10/1/20003.

Claim Objections

Claim 45 is objected to because of the following informalities: the phrase "constructing recombinant plant viral vector each comprising" is grammatically incorrect and should be amended to read "constructing recombinant plant viral vectors each comprising". Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The claimed methods are directed to determination of the presence of a trait in a plant or a change in phenotype or biochemical activity of a plant utilizing an insert from a DNA or RNA library obtained from a non-plant donor where the insert is in an positive sense orientation. At least one unidentified nucleic acid insert obtained from the library is transiently expressed in an infected plant host. The infected plant host is then observed in order to identify any phenotypic or biochemical change that results from expression of the unknown sequence in comparison to a non-infected host plant of the same species.

Claims 45, 60-65 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roninson et al (U.S. Patent No. 5,217,889; see the entire patent) in view of Donson et al (U.S. Patent No. 5,316,931; see the entire patent). Applicants submitted both patents for consideration. **This is a new rejection.**

Roninson et al teach a method of identifying and utilizing genetic suppressor elements (GSEs) for inhibition of gene function (Abstract). Roninson et al teach that functional inactivation (gene suppression) of genes through the expression of specific genetic elements comprising all or a part of the gene to be inactivated is known in the art and can occur through 4 known mechanisms. These mechanisms include inhibition of the target gene-product activity by analogs or fragments of the gene product (i.e. positive sense expression), antisense and ribozyme

interference with translation of the mRNA encoding the target gene product and inhibition of the gene-product mRNA with homologous portions of the mRNA (i.e. positive sense expression) (column 1, lines 20-32). Roninson et al teach that gene suppression is quite useful for scientific studies of gene function and holds considerable promise for certain applications in genetic modification of plants and animals (column 3, lines 1-6). Roninson et al teach that their method can be utilized to modify or improve agricultural plants with regard to viral resistance or elimination of undesirable traits (column 4, lines 10-21). Roninson et al teach that the method of obtaining GSEs requires only the availability of a gene or DNA from a donor organism (plant or animal; e.g. column 4, lines 31-35) and knowledge of a selectable phenotype associated with inactivation of a target gene (column 4, lines 60-67). In the method taught by Roninson et al, DNA corresponding to the gene or genome to be suppressed is randomly fragmented and then inserted into an appropriate vector for the target host cell. Roninson et al teach that the inserted random fragment of donor DNA can be inserted in either a positive sense orientation or in a negative-sense orientation (e.g. in conjunction with a ribozyme sequence) and under control of either a constitutive promoter or inducible promoter (column 5, lines 4-29). Roninson et al then teach that the library can be inserted into the target host cells and the transformed cells screened for the desired phenotype by methods well known in the art (column 5, lines 30-60). Roninson et al also teach that GSEs displaying the desired phenotype can be readily isolated by procedures known in the art (column 6, line 1). Roninson et al teach an example as proof of principle in which phage λ DNA was randomly fragmented, cloned into an expression vector, the vector library then transformed into *E.coli* and the transformants challenged with λ phage to identify transformants having the desired phenotype of resistance to phage λ infection (Examples 2 & 3).

Eleven of the clones isolated in this experiment were further characterized (Example 4). Three of the eleven were found to carry fragments of late genes of phage λ (A, FI and R), inserted in an antisense orientation. The other eight clones contained inserts expected to express sense-strand RNA for the corresponding genes, one of which encoding a full length λ regulatory protein (cro) known to inhibit expression of the early genes of the phage life-cycle. The remaining seven clones were found to only contain DNA fragments corresponding to lambda genes believed to be inessential for phage growth. Six of the remaining clones corresponded to a λ gene of unknown function (Ea8.5), two clones possibly containing the entire coding sequence and four clones having only fragments of the coding sequence for the gene. Roninson et al then identified a host gene associated with the observed trait of resistance to phage λ infection in that when bacteria expressing the Ea8.5 gene are plated on McConkey medium containing maltose they are deficient in maltose uptake, suggesting that inhibition of phage infection occurred through interference with phage absorption via the maltose transport protein, LamB. Thus, this example illustrates that both positive and negative sense expression of a DNA library can be used in the method taught by Roninson et al to identify both host and donor genes associated with a desired trait. Roninson et al further teach an analogous, prophetic example of a similar approach to identify GSEs from a randomly fragmented, total cDNA library derived from TMV which is expressed in tobacco leaf discs and subsequently screened for resistance to TMV infection (example 6).

Roninson et al do not explicitly teach the use of recombinant plant viral vectors to transiently express a heterologous nucleic acid in plants in their methods for identifying genetic suppressor elements. Roninson et al do not explicitly teach the "correlation by observation or

biochemical analysis one or more changes in phenotype or biochemical trait to a plant of the same species that is uninfected" (i.e. use of a negative control plant that is not infected with the recombinant vector).

Donson et al teach the construction and use of plant viral vectors having heterologous subgenomic promoters for the systemic expression of foreign genes in plants. The recombinant plant viral nucleic acids comprise a native plant viral subgenomic promoter, at least one non-native plant viral subgenomic promoter, a plant viral coat protein coding sequence and, optionally, at least one non-native nucleic acid sequence to be transcribed or expressed in the infected host plant. These plant viral vectors are stable, capable of systemic infection and capable of stable transcription or expression of the heterologous nucleic acid sequence in the plant host (e.g. Abstract). The patent teaches that the useful products encoded by the heterologous nucleic acid sequences include proteins, therapeutic proteins (e.g. enzymes) complex biomolecules, ribozymes and/or polypeptides or protein products resulting from anti-sense RNA expression (e.g. column 4, lines 34-42). The product of the heterologous coding sequence may be recovered from the plant or cause a useful phenotype (e.g. male plant sterility, which can be conferred through perturbing mitochondrial function; e.g. column 8, lines 10-12; column 12, lines 9-23; column 17, lines 32-63). The patent teaches that use of the viral vectors of the inventions has a number of advantages, including: 1) transformation and regeneration of target organisms is unnecessary, 2) it is unnecessary to develop vectors which integrate a desired sequence into the genome of the plant (i.e. existing plants can be altered without the need to go through a germ cell), 3) recombinant plant viral nucleic acids are stable for the foreign coding sequences and, 4) the recombinant plant virus vector is capable of systemic infection in the plant

host (column 8, lines 13-26). The patent teaches that a preferred viral type used for constructing the vectors of the invention is tobamovirus group, including the tobacco mosaic virus (e.g. columns 9-10; Example 1). The patent teaches a working example wherein a heterologous protein (i.e. α-trichosanthin) was expressed to ~2% of the total protein in *N. benthamiana* using a TMV vector of the invention (e.g. Example 16, column 40). Donson et al teach this level of expression is as high as what has been reported as maximum levels of expression for heterologous proteins in any genetically engineered plant. Donson et al favorably compare the savings in time and effort obtained by using their methods for systemic infection and expression of the desired gene to conventional Agrobacterium-mediated methods (e.g. less than two weeks as opposed to several months; e.g. column 40, lines 48-63). The recombinant α-trichosanthin produced by the methods of Donson et al is functionally indistinguishable from that produced by conventional methods in T. kirilowii (e.g. column 41, lines 28-41). Finally, the inventors recognize that the rapidity in which results can be obtained (e.g. recovery of α-trichosanthin) would allow for the rapid characterization of improved variants generated by site-directed mutagenesis (e.g. column 41, lines 47-50).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the methods and recombinant plant viral vectors taught by Donson et al into the methods and approach taught by Roninson for identifying genetic suppressor elements. Roninson et al teach it is within the skill of the art to use randomly generated nucleic acids from a donor organism (e.g. a plant) to identify genetic suppressor elements that will yield a desirable phenotype (e.g. male plant sterility) and Donson et al teach it is within the skill of the art to use recombinant plant viral vectors to express desired gene products (e.g. polypeptides, proteins,

enzymes, anti-sense, ribozymes, etc.) in a host plant cell in order to generate a desired phenotype. One would have been motivated to do so in order to receive the expected benefit of rapidly being able to screen, as taught by Donson et al, a large number of different, randomly-generated nucleic acids for their ability to confer the desired phenotype, as taught by both Donson et al and Roninson et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in using the recombinant tobamoviral vectors taught by Donson et al to practice the methods taught by Roninson et al in order to obtain a desired phenotypic trait (e.g. male plant sterility).

With regard to the limitation of "correlating by observation or by biochemical analysis said one or more changes in phenotypic or biochemical traits to a plant host of the same species that is uninfected", it would have been prima facie obvious to practice the methods constructed by the combined teachings of Roninson et al and Donson with a negative control comprising an uninfected plant of the same species. The use of a negative control for comparison of phenotypic and/or biochemical results upon expression of a heterologous sequence in a host cell was routine in the art at the time of the invention. For example, in their working example where genetic suppressor elements were identified for phage lambda, Roninson et al teach the use of a plasmid control lacking the heterologous insert sequence for comparison to test constructs expressing a heterologous sequence in *E. coli*. This teaching correlates with an embodiment of the claimed invention where the results of heterologous sequence expression in an infected host plant cell are compared to a host cell where the heterologous sequence is not expressed (e.g. not infected with a construct expressing a heterologous sequence). Thus, the limitation recited in part (e) of the

rejected claims cannot be considered as nonobvious over the teachings of Roninson et al and Donson et al.

Claims 45, 60-65 and 67-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Roninson et al (U.S. Patent No. 5,217,889; see the entire patent) in view of Kumagai et al (PNAS USA, Vol. 92, pages 1679-1683; see the entire reference). Both references were submitted by applicants for consideration. **This is a new rejection.**

The teachings of Roninson et al are described above and are applied as before, except: Roninson et al do not explicitly teach the use of recombinant plant viral vectors to transiently express a heterologous nucleic acid in plants in their methods for identifying genetic suppressor elements. Roninson et al do not explicitly teach the "correlation by observation or biochemical analysis one or more changes in phenotype or biochemical trait to a plant of the same species that is uninfected" (i.e. use of a negative control plant that is not infected with the recombinant vector).

Kumagai et al teach the use of a tobamoviral vector for the expression of positive sense and antisense fragments of plant genes to manipulate biosynthesis of carotenoids in Nicotiana benthamiana (e.g. Abstract).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the methods and recombinant plant viral vectors taught by Kumagai et al into the methods and approach taught by Roninson for identifying genetic suppressor elements. Roninson et al teach it is within the skill of the art to use randomly generated nucleic acids from a donor organism (e.g. a plant) to identify genetic suppressor elements that will yield a desirable

phenotype (e.g. male plant sterility) and Kumagai et al teach it is within the skill of the art to use recombinant plant viral vectors to express desired gene products (e.g. positive sense polynucleotides) in a host plant cell in order to generate an observable phenotype and manipulate biosynthetic pathways in a plant. One would have been motivated to do so in order to receive the expected benefit of rapidly being able to screen different, randomly-generated nucleic acids for their ability to confer a desired phenotype, as taught by Roninson et al. Absent any evidence to the contrary, there would have been a reasonable expectation of success in using the recombinant tobamoviral vectors taught by Kumagai et al to practice the methods taught by Roninson et al in order to obtain a desired phenotypic trait.

With regard to the limitation of "correlating by observation or by biochemical analysis said one or more changes in phenotypic or biochemical traits to a plant host of the same species that is uninfected", it would have been prima facie obvious to practice the methods constructed by the combined teachings of Roninson et al and Kumagai et al with a negative control comprising an uninfected plant of the same species. The use of a negative control for comparison of phenotypic and/or biochemical results upon expression of a heterologous sequence in a host cell was routine in the art at the time of the invention. For example, in their working example where genetic suppressor elements were identified for phage lambda, Roninson et al teach the use of a plasmid control lacking the heterologous insert sequence for comparison to test constructs expressing a heterologous sequence in *E. coli*. This teaching correlates with an embodiment of the claimed invention where the results of heterologous sequence expression in an infected host plant cell are compared to a host cell where the heterologous sequence is not expressed (e.g. not infected with a construct expressing a heterologous sequence). Similarly,

Kumagai et al explicitly teach the use of uninfected plants for demonstration of a particular phenotype or biochemical change in infected plants due to an expressed heterologous sequence. Thus, the limitation recited in part (e) of the rejected claims cannot be considered as nonobvious over the teachings of Roninson et al and Kumagai et al.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 45, 60-65 and 67-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **The following is a new rejection.**

Claim 45 recites a step (e) wherein one or more changes in phenotypic or biochemical traits of an infected plant are "correlated" to an uninfected plant of the same species. First, it is unclear whether step (e) is a different, additional step since step (d) already recites determining the presence of one or more changes in phenotypic or biochemical traits in an infected plant host. It is unclear how one would determine a change in a phenotypic or biochemical trait in an infected plant without comparison to an uninfected plant (e.g. the same plant prior to infection or a different, uninfected plant). Second, the metes and bounds of the term "correlating" are unclear and are not explicitly defined in the instant specification.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

Ggl

GERRY LEFFERS
PRIMARY EXAMINER